An Urgent Need for Local Guidelines to Address Phosphate Homeostasis in Children with Transfusion-dependent β-thalassemia Major

Sir,

The purpose of this communication is to alert the readers and other relevant stakeholders about a significant problem of a need of local guidelines on the management of metabolic bone disease (MBD) in children with β-thalassemia major (β-TM).

MBDs of multifactorial origin are frequently encountered in the children with β-TM. With a carrier frequency of 6-7% of β-thalassemia gene in the Pakistani population, around 5, 250 infants are born with β-TM annually. Yet, there is no national interest to address bone disorders in these patients. In the last decade, areas of vitamin D, calcium (Ca), and PTH homeostasis in patients with transfusion-dependent β-TM have been researched extensively. However, the effects on phosphate (PO₄) homeostasis are unclear.

Results from our unpublished pilot study revealed that 36.5% (n=134) of transfusion-dependent β-TM children (n=380; age range 5-17 years) had high-serum PO₄ levels (Median= 6.13 mg/dl with IQR of 7-5.7), findings consistent with the study by Tangngam et al., which found asymptomatic hypoparathyroidism in 38% of the β-TM patients. These patients also had significantly lower median plasma fibroblast growth factor-23 (FGF-23) levels than controls. More studies on metabolic bone disease in children with β-TM by the Research Group at our institute show significant growth failure secondary to the iron overload with high-serum ferritin levels, denoting ineffective chelation. High prevalence of bone pains and fragility fractures was significantly associated with hypovitaminosis D, hypocalcaemia, and hyperphosphatemia. Sultan et al. reported altered biochemical markers of bone turnover in regularly transfused thalassemic patients, highlighting a direct correlation between serum PO₄ and ferritin levels. Both hypo- and hyperphosphatemia were seen in the patients. Similarly, in the population studied by Mirhosseini et al., a high prevalence of hypocalcaemia (22%) and hyperphosphatemia (41.7%) suggested the incidence of asymptomatic hypoparathyroidism in patients with β-TM.

Iron overload in β-TM contributes to low-circulating FGF-23 levels, leading to the high PO₄ loading. Physiologically, serum PO₄ is regulated by PTH, vitamin D, FGF-23, and its cofactor Klotho. FGF-23 reduces the formation of 1, 25-(OH)₂D by inhibiting 1 alpha-hydroxylase, and as findings suggest, its impaired response may disrupt PO₄ homeostasis that is furthering a vicious cycle of bone disease. We urge researchers to explore the relation among iron overload, FGF-23, and the Ca-PO₄-PTH axis, so that we can develop local guidelines on the nutritional and pharmacological management of MBD in children with β-TM, which will help in lessening the economic burden of this life-altering disease.

COMPETING INTEREST:
The authors declared no competing interest.

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LJ, AHK: Idea conception, letter revision, and review. AJF: Letter drafting, revision, and review. All the authors have approved the final version of the manuscript to be published.

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Lena Jafri, Arsala Jameel Farooqui and Aysha Habib Khan

Department of Pathology and Laboratory Medicine, The Aga Khan University Hospital, Karachi, Pakistan

Correspondence to: Dr. Lena Jafri, Department of Pathology and Laboratory Medicine, The Aga Khan University Hospital, Karachi, Pakistan
E-mail: lena.jafri@aku.edu

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